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Interactions of Hydroxyurea with a Water Molecule. Ab Initio Molecular Orbital Study

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Ab initio quantum chemical studies at the HF and MP2 levels with the 6-31G** basis set were performed for hydrogen-bonded complexes of hydroxyurea with a water molecule (HUW). Since at both the HF and MP2 levels of theory the keto forms of both *E* and *Z* tautomers of hydroxyurea are found to be much more stable compared to iminol forms, only keto forms were included in our study of HUW. The interaction energies were corrected for the basis set superposition error (BSSE) by using the full Boys−Bernardi counterpoise correction scheme. The zero-point vibrational energies are calculated at the MP2/6-31G**//MP2/6-31G** level. In addition, single-point calculations were performed at the MP2/6-311++G(2df,2pd)//MP2/6-31G** and at the CCSD(T)/6-31G**//MP2/6-31G** levels of theory. It was shown that the complex **I** of HUW is the global minimum on the potential energy surface and also has the largest interaction energy. On the basis of the results of these calculations, the stability of the different conformers of HUW, the nature of the specific hydrogen-bonding interactions, and the interaction energies are discussed.

Introduction

Hydroxyurea or aminoformohydroxamic acid (HU) as a representative of hydroxamic acids has several interesting properties as a specific inhibitor for urea's activity: in patients with chronic leukemia, a complement to radiation treatment in a number of diseases, a selective agent against the episome responsible for drug resistance, stimulators for fetal hemoglobin synthesis reducing the sickle cell anemia episomes, etc. Despite the simple molecular structure of hydroxyurea, this biologically fascinating drug has attracted considerable interest at the academic level and at the clinical stage.[1−12]

Hydroxyurea can exist in two main tautomeric forms: keto and iminol tautomers. In both forms the hydroxyl group can be present in either trans or cis orientation (denoted as *E* and *Z*, respectively, Figure 1). HU and its derivatives have been the subject of recent theoretical and experimental studies, since all of these molecules are important model systems because of the potential hydrogen-bonding and acid−base properties associated with their functional groups.[13−20] The focus has primarily been on explaining the conformational equilibrium and to provide a more accurate understanding of the molecular parameters and properties of these molecules. Analysis of X-ray diffraction of crystals of formohydroxamic acid and the hemihadrate of acetohydroxamic acid shows that they exist in the *Z* keto form, corresponding to the formation of intramolecular H-bonding between the O atom of the carbonyl and the H atom of the hydroxyl group.[14,15] According to NMR studies, monoalkylhydroxamic acids exist in both *E* and *Z* keto as well as iminol forms.[16] Previous theoretical studies on the related systems include INDO,[17] AM1, PM3,[13] and ab initio calculations[13,18] on formohydroxamic acid, ab initio calculations on tetramethylurea, tetramethylthiourea[19] and on hydrogen-bonded complexes of urea with two water or two hydrogen fluoride and on ethylenurea with two water molecules[20] and, more recently, ab initio calculations on hydroxyurea.[9] However, to our knowledge, no calculations have been reported for hydroxyurea complexes with a water molecule.

We present in this paper the results of quantum chemical ab initio study of hydroxyurea complexes with a water molecule (HUW). Since at both the Hartree−Fock (HF) and the second-order Møller−Plesset perturbation (MP2) levels of theory the keto forms of both *E* and *Z* species of HU are found to be much more stable, only such keto forms were included in our study of HUW. It is worth noting that this model system contains a segment of the structural (NCO) group similar to those in proteins, and there is a justified speculation that this similarity might be connected to the observed biological activities.[1,6−8] Therefore, such a theoretical study can provide valuable information on hydroxyurea's aqueous environment and physicochemical properties and might be helpful in better understanding some its related biological activity. On the basis of the results of these calculations, the stability of the different conformers of HUW, the nature of the specific hydrogen-bonding interactions, and the interaction energies are discussed.

Method

The ab initio molecular orbital calculations were performed using Gaussian92 and Gaussian94 program packages.[21] Geometry optimizations of the hydrogen-bonded different complexes of HU were carried out at the HF and MP2 levels of the theory using the standard split-valence 6-31G** basis set. The single-point calculations were also carried out at the MP2/6-31G**//MP2/6-31G** optimized geometry using the second-order many-body perturbation theory with the 6-311++G(2df, 2pd) basis set (i.e., MP2/6-311++G(2df,2pd)//MP2/6-31G**). The frozen-core approximation was kept throughout. Zero-point vibrational energies calculated at the MP2/6-31G**//MP2/6-31G** level were corrected using a scaling factor of 0.95.[22] The interaction energies for the complexes of HUW were corrected for the basis set superposition error (BSSE) by using the full Boys−Bernardi counterpoise correction scheme.[23,24]

Results and Discussion

1. Geometries and Relative Energies. Although the geometries of the different tautomers of HU shown in Figure 1 are not presented here in detail, we would like to comment on

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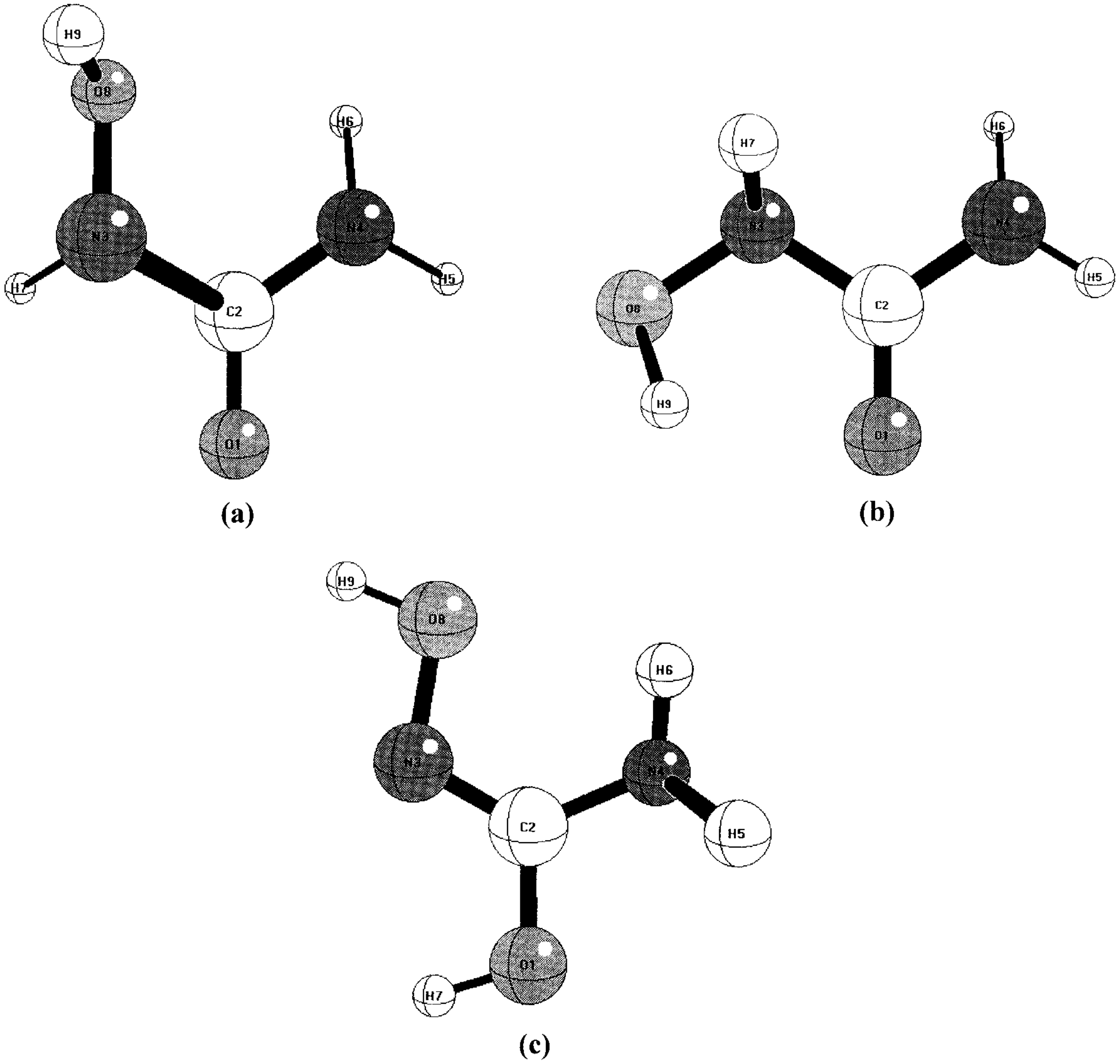

Figure 1. Different tautomers of HU: (a) *E* keto form, (b) *Z* keto form, (c) *E* iminol form.

the predicted nonplanarity of this species. Originally, the structures of urea derivatives were believed to be planar due to the partial double-bond character of the C−N bond.[25] Experimental X-ray and neutron-diffraction data has confirmed the planar structure of the urea molecule in the crystal phase while in the gas phase its microwave spectrum indicates a nonplanar structure.[26,27] The ab initio study on urea[20,28] and formohydroxyurea,[13] the present data, and the other ab initio[9] studies on HU show that the nonplanar structure for these molecules are more energetically favorable than the planar structures. For example at the HF/6-31G**//HF/6-31G** level, the nonplanar conformers of HU in the *E* and the *Z* keto forms lie 11.0 and 3.9 kcal/mol lower than the planar structures, respectively. Taking this and the fact that the keto forms of HU are much more energetically profitable at both the HF and MP2 levels of theory compared to the possible iminol forms into account, only such keto isomers were included in our study of HUW. Thus, for example, the closest in energy of the iminol form of HU which can be obtained from the *E* keto form by abstracting the H atom from the imino group and connecting it to carbonyl oxygen lie more than 13 kcal/mol higher than the global minima at the HF/6-31G**//HF/6-31G** level. The other possible iminol forms of HU have even higher relative energies (more than 20 kcal/mol) at the same level of theory.

A number of possible complexes of HUW have been considered in this study. A sketch of some important complexes of HUW is shown in Figure 2, where the numbering of the atoms is also defined. The complexes **I**−**IV** of HUW can be easily obtained via interaction of the *E* keto form of HU with the water molecule while the complexes **V**−**VII** correspond to similar interactions of the *Z* keto form (Figure 2). The optimized bond distances, bond angles, and the major dihedral angles of these complexes of HUW are collected in Tables 1 and 2. Tables 3 and 4 show the energetic characteristics of these complexes optimized at the HF and MP2 levels of the theory, respectively. Note that Table 4 also contains the zero-point vibrational energies calculated at the MP2/6-31G**//MP2/6-31G** level for the most important forms (**I**−**V**) of HUW. The results are clearly dependent upon the levels of calculation. At all applied levels of theory, structure **I** is found to be the global minimum at the potential energy surface (PES). It has a ringlike structure and is stabilized via formation of two H bonds: one bond is between the H atom of the water molecule and the O atom of the carbonyl group of HU, and the other bond is between the H atom of the amino group of HU and the O atom of the water molecule (Figure 2a). The former bond is found to be relatively shorter than the latter one indicating a relatively strong proton acceptor ability for the carbonyl oxygen of HU compared to the water oxygen in this complex (cf. also the distances of $O_{10}(H_{11})$−X and O_{10}−(H)Y between the heteroatoms involved in these H bonds, see Table 1). Both the NH···O and the OH···O bonds are strongly bent. Such bent H

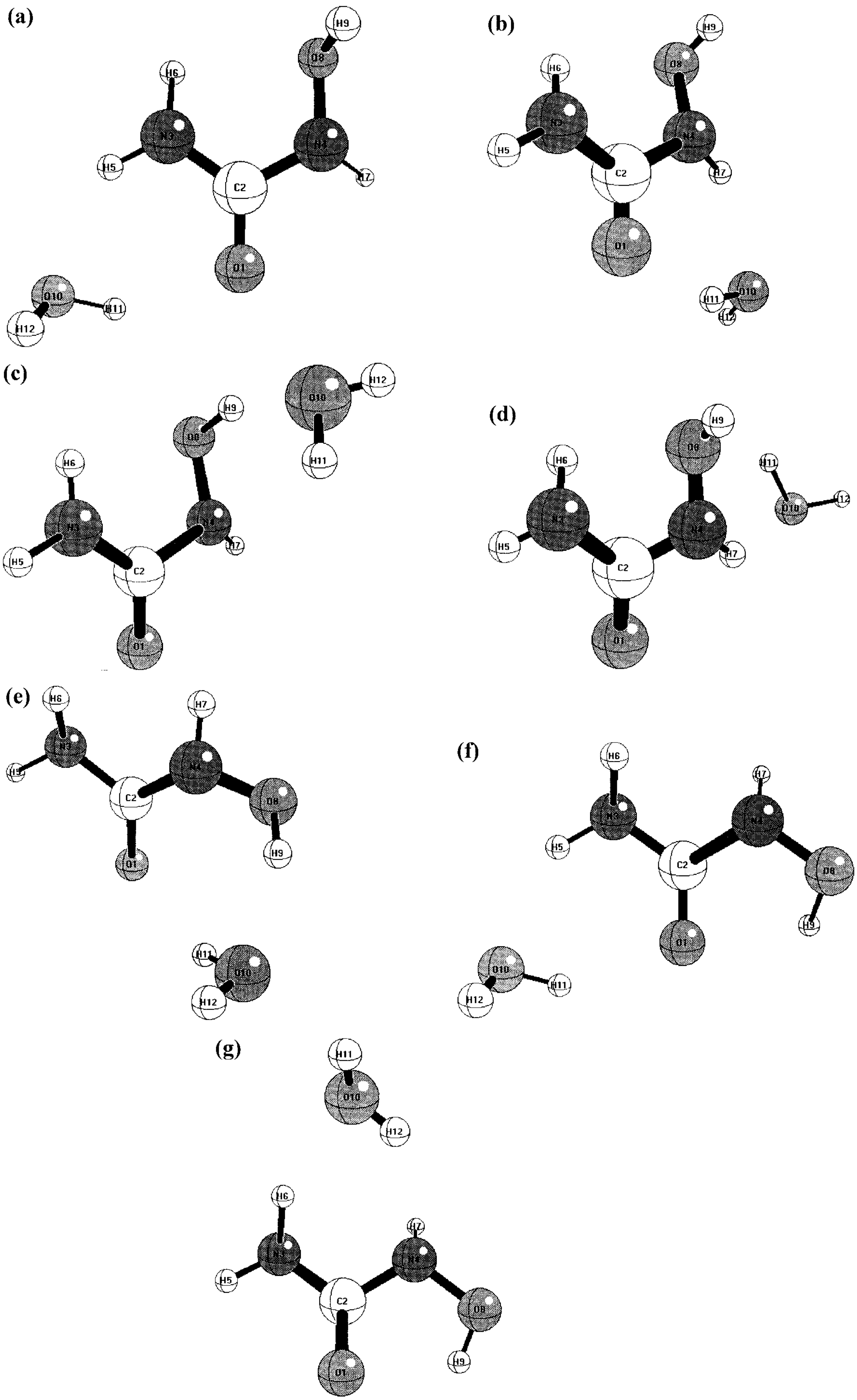

Figure 2. Different complexes of HUW considered in this study: (a) complex **I**, (b) complex **II**, (c) complex **III**, (d) complex **IV**, (e) complex **V**, (f) complex **VI**, (g) complex **VII**.

TABLE 1: Bond Distances (Å) for Different Complexes (I−VII) of Hydroxyurea with a Water Molecule Optimized at the HF/6-31G//HF/6-31G** and the MP2/6-31G**//MP2/6-31G** Levels of Theory[a]**

	I	II	III	IV	V	VI	VII
O_1-C_2	1.208 (1.237)	1.208 (1.237)	1.199 (1.225)	1.197 (1.224)	1.201 (1.231)	1.209	1.201
C_2-N_3	1.339 (1.351)	1.345 (1.362)	1.349 (1.362)	1.353 (1.370)	1.362 (1.379)	1.347	1.349
C_2-N_4	1.389 (1.412)	1.380 (1.399)	1.392 (1.423)	1.391 (1.416)	1.379 (1.398)	1.381	1.397
N_3-H_5	0.998 (1.014)	0.992 (1.005)	0.992 (1.005)	0.993 (1.006)	0.994 (1.007)	0.999	0.994
N_3-H_6	0.991 (1.005)	0.991 (1.005)	0.992 (1.006)	0.991 (1.006)	0.993 (1.007)	0.993	0.998
N_4-H_7	0.998 (1.015)	1.002 (1.021)	0.998 (1.016)	1.001 (1.019)	0.996 (1.012)	0.999	1.001
N_4-O_8	1.381 (1.430)	1.381 (1.428)	1.382 (1.431)	1.389 (1.442)	1.375 (1.417)	1.380	1.382
O_8-H_9	0.945 (0.967)	0.945 (0.967)	0.952 (0.979)	0.945 (0.967)	0.952 (0.981)	0.951	0.952
$O_{10}(H_{11})-X^b$	2.882 (2.826)	2.877 (2.819)	3.103 (2.873)	2.990 (2.881)	2.898 (2.824)	2.903	
$H\cdots O_{10}$	2.157 (2.025)	2.147 (2.012)	1.933 (1.856)	2.210 (2.111)	1.950 (1.811)	2.129	2.135
$O_{10}-(H)Y^c$	3.008 (2.896)	3.010 (2.902)	2.826 (2.741)	2.988 (2.912)	2.799 (2.718)	2.994	3.031
$O\cdots H_{11}$	2.028 (1.935)	2.040 (1.944)		2.387 (2.138)	2.050 (1.930)	2.074	
$O_{10}-H_{11}$	0.951 (0.970)	0.951 (0.973)	0.945 (0.969)	0.945 (0.966)	0.951 (0.974)	0.950	0.946
$O_{10}-H_{12}$	0.943 (0.962)	0.943 (0.963)	0.944 (0.963)	0.943 (0.962)	0.943 (0.963)	0.943	0.943

[a] The data related to the MP2/6-31G**//MP2/6-31G** calculations are given in parentheses. [b] Hydrogen bond distance in which the X heteroatom of HU acts as a proton acceptor from the water molecule. [c] Hydrogen bond distance in which the Y heteroatom of HU acts as a proton donor to the water molecule.

TABLE 2: Bond Angles and Dihedral Angles (deg) for Different Complexes (I−VII) of Hydroxyurea with a Water Molecule Optimized at the HF/6-31G//HF/6-31G** and the MP2/6-31G**//MP2/6-31G** Levels of Theory[a]**

	I	II	III	IV	V	VI	VII
$O_1-C_2-N_3$	125.0 (126.0)	123.6 (124.2)	124.8 (126.3)	124.5 (125.6)	122.7 (122.9)	124.5	125.3
$O_1-C_2-N_4$	118.5 (118.3)	120.1 (120.4)	119.7 (119.8)	119.7 (119.6)	123.5 (123.9)	121.1	121.2
$C_2-N_3-H_5$	116.5 (115.0)	116.3 (115.0)	115.9 (115.1)	115.2 (113.8)	114.9 (113.5)	116.0	115.3
$C_2-N_3-H_6$	119.9 (117.7)	120.2 (117.4)	119.5 (116.9)	119.6 (117.0)	120.2 (118.3)	119.3	119.0
$C_2-N_4-H_7$	111.5 (109.3)	113.1 (111.0)	110.6 (108.0)	112.5 (110.3)	115.7 (113.8)	113.9	112.1
$C_2-N_4-O_8$	115.4 (117.7)	115.4 (113.5)	115.4 (113.3)	115.1 (113.0)	115.4 (114.3)	114.0	112.9
$N_4-O_8-H_9$	105.3 (102.2)	105.3 (102.3)	104.4 (100.8)	105.0 (101.9)	105.9 (102.8)	105.6	105.4
$O_{10}-H_{11}\cdots O$	148.5 (151.0)	145.9 (148.3)		121.4 (132.6)	147.6 (151.4)	144.9	
$O_{10}\cdots HN(\text{or } O)$	142.1 (142.6)	143.2 (144.1)		133.6 (133.9)	147.3 (152.5)	143.9	
$H\cdots O_{10}-H_{11}$	78.1 (79.0)	78.0 (78.2)	96.0 (82.7)	83.7 (76.5)	84.1 (83.7)	80.3	92.2
$H_{11}-O_{10}-H_{12}$	106.0 (103.8)	106.1 (103.9)	106.7 (104.5)	106.8 (104.6)	106.4 (104.2)	106.3	107.2
$O_1-C_2-N_3-N_4$	−176.4 (−174.0)	−176.5 (−174.0)	−175.9 (−173.6)	−175.9 (−173.3)	−177.1 (−176.7)	179.5	179.4
$O_1-C_2-N_3-H_5$	6.8 (11.3)	7.5 (14.0)	9.8 (14.4)	10.2 (15.2)	−12.4 (−16.8)	−8.3	−8.1
$O_1-C_2-N_4-H_7$	−33.5 (−37.6)	−31.6 (−34.7)	−33.3 (−36.7)	−36.2 (−41.6)	−153.1 (−151.6)	−132.2	−128.6

[a] The data related to the MP2/6-31G**//MP2/6-31G** calculations are given in parentheses.

TABLE 3: Total Energies (au), Relative Energies (E_{rel}, kcal/mol), and Interaction Energies (E_{int}, kcal/mol) of Different Complexes (I−VII) of Hydroxyurea with a Water Molecule As Calculated by ab Initio at the HF/6-31G//HF/6-31G** and the MP2/6-31G**//HF/6-31G** Levels of Theory**

	I	II	III	IV	V	VI	VII
HF/6-31G**//HF/6-31G**	−374.83541	−374.83487	−374.83287	−374.82704	−374.83003	−374.82844	−374.82617
$E_{rel.}$	0.0	0.34	1.59	5.25	3.38	4.37	5.80
$-E_{int}{}^a$	10.2	9.9	8.6	5.0	10.6	9.6	8.2
$-E_{int}{}^b$	7.8	7.5	6.8	3.1	8.8	7.5	6.4
MP2/6-31G**//HF/6-31G**	−375.85364	−375.85287	−375.85073	−375.84444	−375.84853	−375.84758	−375.84555
E_{rel}	0.0	0.48	1.83	5.78	3.20	3.80	5.07
$-E_{int}{}^a$	9.1	8.6	7.2	3.3	9.0	8.4	7.1

[a] Interaction energies are not corrected for the BSSE. [b] Interaction energies are corrected for the BSSE.

bonds are not exceptional[29] although usually for bimolecular H-bonded complexes the hydrogen bond angle is expected to be close to 180°.[30,31]

The next complex of HUW (**II**) also possesses a ringlike structure in which imino group of HU acts as a proton donor to the water molecule and the carbonyl oxygen act as proton acceptor from the water molecule (Figure 2b). It is only ca. 0.5 kcal/mol less stable than the complex **I**. The proton acceptor ability of the carbonyl oxygen in the complex **II** still remains a little more favorable compared to that of the water oxygen since the $O_{10}-O_1$ distance is much shorter (more than 0.13 and 0.08 Å, respectively, at the HF and MP2 levels of theory) than the $O_{10}-N_4$ one (see Table 1). Both the NH···O and the OH···O bonds are strongly bent and differ slightly from those of the complex **I**. As could be expected, the calculated O−H bond length for the free hydroxyl group is shorter and stronger than that involved in the H bond for the water fragment in both complexes **I** and **II**. Note that the intramolecular H bond formed between the H atom of the amino group and the O atom of the hydroxyl group attached to the imino group is the weakest one for complexes of **I** and **II** as is apparent from the calculated bond distances.

In contrast to the complexes **I** and **II**, complex **III** is stabilized by the formation of a relatively stronger single H bond in which the water oxygen acts as a proton acceptor from the hydroxyl group of HU (Figure 2c). Surprisingly, even this bond is not linear and deviates from linearity by ca. 30° at the HF and MP2 levels of theory. Note, however, in the MP2 level of theory the N atom of the imino group of HU forms an additional very weak bond with the H atom of the water molecule (it became four-coordinated). At the HF level this bond length is equal to 2.785 Å, while at the MP2 level it amounts only to 2.259 Å. Such a large discrepancy between the HF and the MP2 levels of theory deserves additional comments. It is not an artefact

TABLE 4: Total Energies (au), Relative Energies (E_{rel}, kcal/mol), Interaction Energies (E_{int}, kcal/mol), Zero-Point Vibrational Energies (ZPE, au), and Zero-Point Vibrational Energy Corrections (ΔZPE, kcal/mol) of Different Complexes (I−V) of Hydroxyurea with a Water Molecule As Calculated by ab Initio at the MP2/6-31G//MP2/6-31G** and the MP2/6-311++G(2df,2pd)// MP2/6-31G** Levels of Theory**

	I	II	III	IV	V
MP2/6-31G**//MP2/6-31G**	−375.85942	−375.85863	−375.85737	−375.85064	−375.85429
$E_{rel.}$	0.0	0.50	1.29	5.51	3.22
$-E_{int}{}^{a}$	12.7	12.2	11.4	7.2	12.6
$-E_{int}{}^{b}$	8.5	7.9	7.8	3.7	9.5
ZPE^{c}	0.09089	0.09069	0.09065	0.08994	0.09078
ΔZPE	2.5	2.4	2.3	1.9	2.8
MP2/6-311++G(2df,2pd)//MP2/6-31G**	−376.27602	−376.27545	−376.27392	−376.26790	−376.27126
E_{rel}	0.0	0.36	1.32	5.10	2.99
$-E_{int}{}^{a}$	10.3	9.9	8.9	5.1	9.8
$-E_{int}{}^{b}$	8.9	8.4	7.6	4.0	8.0

[a] Interaction energies are not corrected for the BSSE. [b] Interaction energies are corrected for the BSSE. [c] The ZPE's for the isolated *cis*-, and *trans*-hydroxyurea and the water molecule amounts 0.06617, 0.06556, and 0.02078 au, respectively, at the MP2/6-31G**//MP2/6-31G** level of theory.

TABLE 5: Effective Atomic Charges (Q, $|e^-|$) and Dipole Moments (D, D) of Different Complexes (I−V) of Hydroxyurea with a Water Molecule As Calculated by ab Initio at the MP2/6-31G//MP2/6-31G** Level of Theory**

	Q_{O1}	Q_{C2}	Q_{N3}	Q_{N4}	Q_{H5}	Q_{H6}	Q_{H7}	Q_{O8}	Q_{H9}	Q_{O10}	Q_{H11}	Q_{H12}	D
I	−0.6836	0.9374	−0.7751	−0.3656	0.3643	0.3338	0.3292	−0.5224	0.3795	−0.7237	0.3896	0.3367	3.527
II	−0.6806	0.9357	−0.7489	−0.3923	0.3250	0.3356	0.3673	−0.5252	0.3793	−0.7217	0.3894	0.3365	3.824
III	−0.6270	0.9022	−0.7480	−0.4059	0.3235	0.3390	0.3256	−0.5487	0.4093	−0.7003	0.3790	0.3513	2.754
IV	−0.6186	0.9055	−0.7514	−0.3776	0.3222	0.3279	0.3549	−0.5550	0.3805	−0.6954	0.3651	0.3419	5.385
V	−0.6604	0.9438	−0.7547	−0.4002	0.3271	0.3107	0.3157	−0.5154	0.4183	−0.7261	0.4005	0.3407	5.473

TABLE 6: Effective Atomic Charges (Q, $|e^-|$) and Dipole Moments (D, D) of Different Complexes (I−V) of Hydroxyurea with the Water Molecule As Calculated by ab Initio at the MP2/6-311++G(2df,2pd)//MP2/6-31G Level of Theory**

	Q_{O1}	Q_{C2}	Q_{N3}	Q_{N4}	Q_{H5}	Q_{H6}	Q_{H7}	Q_{O8}	Q_{H9}	Q_{O10}	Q_{H11}	Q_{H12}	D
I	−.6117	0.5463	−0.2821	−0.2325	0.2165	0.1385	0.1586	−0.1528	0.2223	−0.4187	0.2323	0.1832	3.628
II	−0.6146	0.5603	−0.2960	−0.2250	0.1358	0.1175	0.2329	−0.1382	0.2283	−0.4167	0.2355	0.1803	3.882
III	−0.5545	0.4918	−0.2569	−0.2120	0.1328	0.1229	0.1672	−0.1870	0.2720	−0.3756	0.2121	0.1871	2.865
IV	−0.5461	0.5166	−0.2747	−0.2163	0.1303	0.1129	0.2118	−0.1725	0.2248	−0.3708	0.2032	0.1809	5.344
V	−0.5877	0.5531	−0.2227	−0.1910	0.1364	0.0964	0.1203	−0.2303	0.3242	−0.4277	0.2492	0.1799	5.326

of the calculations, since we start the optimization at both levels of theory using one and the same initial trial geometry for complex **III**. However, the respective optimized structures differ from one another (Tables 1 and 2). We took the optimized structure at the MP2 level of theory as a starting test geometry for the HF case and vice versa; we also took the optimized structure at the HF level of theory as a trial geometry for the MP2 case, and they were also fully optimized. These latter optimized geometries for the complex **III** exactly coincide with the previously obtained optimized geometries within the MP2 or the HF levels of theory, respectively.

The final considered structure of HU in the *E* keto form interacting with the water molecule is the complex **IV** (Figure 2d). It is stabilized by the formation of two relatively weak H bonds. At both levels of theory, the NH···O bond is slightly shorter than the OH···O bond formed between the H atom of the water molecule and the O atom attached to the imino group of HU. Among complexes **I**−**IV** of HUW in which HU is in the *E* keto form, complex **IV** is the less stable one (it lies more than 5 kcal/mol higher in energy than the global minimum corresponding to the complex **I**). It is not surprising since at both levels of theory this complex has relatively the largest H bond distances due to the fact that the proton acceptor ability of the O atom attached to the imino group of HU is weaker than that of the water oxygen. In this sense, hydrogen from the hydroxyl group connected to the imino group has the highest acidity in complex **IV**. As a simple measure, such a phenomenon is related to the net atomic Mulliken charges presented in Tables 5 and 6 for the HF and MP2 levels of theory, respectively.

Among the last structures considered (**V**−**VII**), complex **V** is the most important one (Figure 2e) since it is formed by the interaction of HU in the *Z* keto form with the water molecule and lies close to complex **I** on the PES (ca. 3 kcal/mol higher in energy than the complex **I**). This ringlike structure is stabilized by formation of two relatively strong OH···O bonds which have the shortest H bond distances among the structures **I**−**VII**. In the first OH···O bond, the O atom of the water acts as a proton acceptor from the hydroxyl group of HU, and in the second case, the carbonyl oxygen acts as a proton acceptor from the water molecule. Both bonds deviate strongly from linearity. Note that the former bond is shorter than the latter one due to the fact that HU is a relatively stronger nitrogen acid than water. The effective Mulliken charge on the H_9 atom is the largest one among other H atoms within complex **V** (see Tables 5 and 6).

These findings support the idea that the hydration of a carbonyl group, which is a reaction of some importance in organic chemistry and biochemistry,[32,33] proceeds also via a cooperative (cyclic) mechanism in the case of HU. However, it is in contrast to the uncatalyzed addition of water to formaldehyde for which up to two additional water molecules could play an intimate role in the neutral hydration of a carbonyl group with the formation of a cyclic eight-membered reaction complex.[34] The reason for this is that HU has much more acidic hydrogens compared to those of formaldehyde. Probably the keto−iminol tautomerism of HU will also be easily enhanced by interactions with water if one takes into account at least one water molecule.

It is also worth noting that all of these complexes of HUW considered in this study remain nonplanar as the HU molecule in both the *E* or *Z* keto forms, even if one takes into consideration only the N(CO)N moiety instead of the whole complex (see Table 2, dihedral angles). This is in line with the other ab initio study on formohydroxyurea[13] and on HU,[9] but it is in contrast with the conclusions of Ramondo et al.,[20] according to which the N(CO)N moiety is always planar for a urea molecule in the three different conformers. These results are due to the use of the small, unreliable 3-21G and 4-31G(d) basis sets, and more probably, it was fixed *a priori* as a planar.[20]

2. Interaction Energies. The HF/6-31G**//HF/6-31G** and the single-point MP2/6-31G**//HF/6-31G** calculations show that interaction energies calculated as the energy difference between the complex and the sum of isolated monomers at the respective optimal geometry for complexes **I** and **V** are the relatively highest among the considered structures (Table 3). The MP2/6-31G**//MP2/6-31G** level of theory virtually does not change the order of these interaction energies (Table 4). As could be expected, the BSSE corrections significantly lowered these interaction energies (Table 3 and 4) and complex **V** became a little more favorable than complex **I** at the both levels of theory. We shall note that we use the standard Boys–Bernardi counterpoise correction scheme[23] for BSSE taking into account also the geometry reorganization when going from the isolated subsystems to the complex as is discussed in the refs 24 and 35. However this order changes when one uses an extended basis set. For example, the MP2/6-311++G(2df, 2pd)// MP2/6-31G** single-point calculations with inclusion of BSSE corrections shows that complex **I** has the highest interaction energy among these structures. The BSSE corrections are different at the HF and the MP2 levels of theory: when one uses the same basis set, the BSSE is higher at the correlated level of theory (see Table 4). These BSSE-corrected interaction energies for complexes **I** and **V** of HUW are significantly larger than those for both the cyclic water–hydroxylamine complex and the four-membered cyclic water and ammonia dimers at the same correlated MP2 level of theory[36] or those for the water–formaldehyde complexes at the different levels of the theory.[29]

There is some direct correlation between these interaction energies and the net atomic charges on the O_{10} and H_{11} atoms of the water molecule involved in the H bonds of these complexes. It appears that, within the initial *E* or *Z* keto forms, the absolute value of the charge on both O_{10} and H_{11} atoms is directly proportional to the interaction energy. However, there is no correlations between dipole moments of these complexes and their interaction energies (see Tables 5 and 6).

Zero-point vibrational energies (ZPE) and ΔZPE calculated at MP2/6-31G**//MP2/6-31G** level of theory are also presented in Table 4 for the complexes **I**–**V** of HUW. The latter ΔZPE are calculated as the ZPE difference between the complex and the sum of isolated monomers. The most pronounced effect of incorporating the ΔZPE corrections is the lowering of both the total energy and the interaction energy of complex V compared to that of complex **I**. If one takes into account these factors, then complex **I** of HUW is not only the global minima on the PES but also has the largest interaction energy. To further support this statement, we performed coupled-cluster calculations using both single and double substitutions from the Hartree–Fock determinant, with noniterative inclusion also of triple excitations (CCSD(T)) for the most important complexes **I**–**III** and **V** of HUW. Table 7 shows the energetic characteristics of these complexes calculated at the CCSD(T) level of theory using the respective MP2/6-31G**//MP2/6-31G**-optimized geometries. As is clear at higher levels of the theory, the complex **I** of HUW has both the lowest energy on the PES and the largest interaction energy.

TABLE 7: Total Energies (au), Relative Energies (E_{rel}, kcal/mol), and Interaction Energies Corrected for the BSSE (E_{int}, kcal/mol) of Complexes I, II, III, and V of Hydroxyurea with Water Molecule As Calculated at the CCSD(T)/6-31G//MP2/6-31G** Level of Theory**

	I	II	III	V
CCSD(T)/6-31G**// MP2/6-31G**	−375.92203	−375.91943	−375.91796	−375.91509
E_{rel}	0	1.63	2.56	4.35
E_{int}	9.4	7.6	7.3	9.1

Conclusions

The ab initio results at the HF/6-31G**//HF/6-31G** and MP2/6-31G**//HF/6-31G** level of theory show that interaction energies for complexes **I** and **V** are the highest among the different structures of HUW considered in this study. MP2/6-31G**//MP2/6-31G** level of theory does not virtually change the order of these interaction energies. However, the inclusion of the BSSE and ΔZPE corrections results in significantly lowered interaction energies between these complexes of HUW. The use of an extended 6-311++G(2df,2pd) basis set for the single-point calculations at the correlated MP2/6-311++G(2df, 2pd)//MP2/6-31G** level with the BSSE corrections changes the stability order. At this and at the CCSD(T)/6-31G**//MP2/6-31G** levels of theory, structure **I** is predicted to be the most stable and also has the highest interaction energy among these structures. Moreover, there is direct correlation between the interaction energy and the net atomic charges on the O_{10} or H_{11} atoms of the water molecule involved in the H-bonding: within the initial *E* or *Z* keto forms, the higher the absolute value of the charge on both O_{10} and H_{11} atoms, the higher the interaction energy.

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References and Notes

(1) Thurman, W. G.; Bloedow, C.; Howe, C. D. *Cancer Chemother. Rep.* **1963**, *29*, 103.
(2) Griffith, K. *Cancer Chemother. Rep.* **1964**, *40*, 47.
(3) Stearns, B.; Losee, K.; Bernstein, J. *J. Med. Pharm. Chem.* **1963**, *6*, 201.
(4) Fishbein, W.; Carbone, P. *Science* **1963**, *142*, 1069.
(5) Bendich, A.; Borenfreund, E.; Korngold, G.; Krim, M. *J. Nat. Cancer Inst.* **1964**, *32*, 667.
(6) Christen, R. D.; Shalinski, D. R.; Howell, S. B. *Proc. Am. Soc. Clin. Oncol.* **1990**, *9*, 210.
(7) Riendeau, D.; Falgueyret, J. P; Guay, J.; Ueda, N.; Yamamoto, S. *Biochem. J.* **1991**, *274*, 287.
(8) Berkenkopf, J. W.; Weichman, B. M. *Eur. J. Pharmocol.* **1991**, *193*, 29.
(9) LaManna, G.; Barone, G. *Intern. J. Quantum Chem.* **1996**, *57*, 971.
(10) Lipczynska-Kochany, E. *Chem. Rev.* **1991**, *91*, 477.
(11) Kobashi, K.; Terashima, N.; Hase, J. *Chem. Pharm. Bull.* **1973**, *21*, 2303.
(12) von Hoff, D.; Forset, B.; Bradly, T. *Proc. Am. Soc. Clin. Oncol.* **1990**, *9*, 209.
(13) Turi, L.; Dannenberg, J. J.; Rama, J.; Ventura, O. N. *J. Phys. Chem.* **1992**, *96*, 3709.
(14) Larsen, I. K. *Acta Crystallogr. B*, **1988**, *44*, 527.
(15) Brecher, B. H; Small, R. W. H. *Acta Crystallogr. B*, **1970**, *26*, 1705.

(16) Lipczynska-Kochany, E.; Iwamura, H. *J. Org. Chem.* **1982**, *47*, 5277.

(17) Hilal, R.; Moustafa, H. *Intern. J. Quantum. Chem.* **1984**, *26*, 183.

(18) Fitzpatrick, N. J.; Mageswaran, R. *Polyhedron* **1989**, *8*, 2255.

(19) Tóth, K.; Bopp, Ph.; Peräkylä, M.; Pakkanen, T.; Jancsó, G. *J. Mol. Struct. (Theochem)* **1994**, *312*, 93.

(20) Ramondo, F.; Bencivenni, L.; Rossi, V.; Caminiti R. *J. Mol. Struct. (Theochem)* **1992**, *227*, 185.

(21) (a) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. V.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Rob, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Rghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *GAUSSIAN 92*; Gaussian Inc.: Pittsburgh, PA, 1992. (b) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; and Pople, J. A. *GAUSSIAN 94*, Revision D.3, Gaussian, Inc., Pittsburgh PA, 1995.

(22) Venkatraman, R.; Nowek, A.; Leszczynski, J. *J. Phys. Chem.* **1996**, *100*, 11616.

(23) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

(24) Mayer, I.; Surjan, P. R. *Chem. Phys. Lett.* **1992**, *191*, 497.

(25) Ormerod, M. B. *The Architecture and Properties of Matter*, Fletcher and Sons: Norwich, 1970.

(26) (a) Vaughan, P.; Donohue J. *Acta Crystallogr.* **1952**, *5*, 530. (b) Worsham, J. E.; Levy, H. A.; Peterson, S. W. *Acta Crystallogr.* **1957**, *10*, 319.

(27) Brown, R. D.; Godfrey, P. D.; Storey, J. *J. Mol. Spectrosc.* **1975**, *58*, 445.

(28) Meier, R. J.; Coussens, B. *J. Mol. Struct. (Theochem)* **1992**, *253*, 25.

(29) Ramelot, T. A.; Hu, Ch.-H.; Fowler, J. E.; DeLeeuw, B. J. *J. Chem. Phys*. **1994**, *100*, 4347.

(30) Hobza, P.; Zahradnìk, R. *Weak Intermolecular Interactions in Chemistry and Biology*, Elsevier, Amsterdam, **1980**.

(31) Jorgenson, W. L.; Swensen, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1489.

(32) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1.

(33) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; Dover Publications, Inc.: New York, 1987.

(34) Wolfe, S.; Kim, C.-K.; Yang, K.; Weinberg, N.; Shi, Z. *J. Am. Chem. Soc.* **1995**, *117*, 4240.

(35) Florian J., Leszczynski, J. *J. Am. Chem. Soc.* **1996**, *118*, 3011.

(36) Yeo, G. A.; Ford, T. A. *J. Mol. Struct. (Theochem)* **1991**, *235*, 123.